Observations on the Effects of a New Diuretic — S1520

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SUMMARY

S1520, a sulphonamide-derived diuretic, was administered to healthy volunteers and patients with oedema. A therapeutic effect was produced by doses of 10 - 20 mg. The onset of action was within 3 hours and persisted for up to 36 hours. Natriuresis, chloruresis and increasing kaliuresis were observed with continued administration. The probable site of drug action was on the distal tubule. Patients with severe renal failure or hyponatraemia did not show a therapeutic response, and the maximal efficacy of the drug was considered to be less than that of furosemide.

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S1520 is a sulphonamide-derived diuretic developed by Servier Laboratories of Paris. The chemical name is N-(3-sulphonamoyl-4-chlorobenzamido)-2-methyl indoline, with the structural formula shown in Fig. 1. Animal

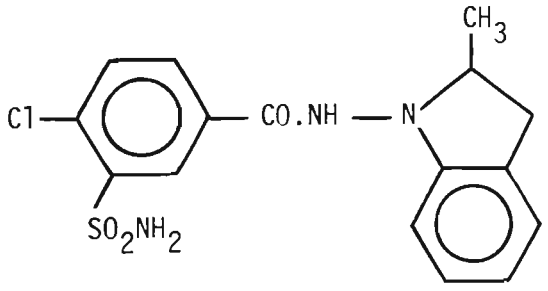

Fig. 1. The structural formula of S1520.

experiments and initial clinical studies in France indicate that the drug is potent, effective, and of low toxicity.

This article presents the results of studies done on normal volunteers to determine the therapeutic dose, duration of action, water and electrolyte excretion, the site of action of the drug, and its therapeutic effect in patients with oedema.

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NORMAL SUBJECTS

Potency and Duration of Action

Five normal subjects on their usual diet, were studied. Urine for a control period of 48 hours was collected in a series of separate samples as they were voided. Volume, osmolality, sodium and potassium content of each specimen were estimated, and the excretion expressed as ml/min, mOsm/min, and mEq/min. A single oral dose of S1520 was then given and measurements were made for a further 48 hours. At intervals of 1 week, to allow for full repletion of fluid and electrolytes, the procedure was repeated with increasing doses of S1520 in an attempt to determine minimal and maximal effective doses of the drug. A measurable natriuresis was noted in all 5 subjects after the administration of as little as 2,5 mg (± 0,3 mg/kg), although urinary volumes were not consistently increased. Effective sodium and water diuresis occurred regularly with doses of 10 mg (± 0,14 mg/kg), or more. Maximal efficacy was achieved with doses of 40 mg (± 0,57 mg/kg), but the response to this dosage was only marginally greater than that achieved by 20 mg. The onset of diuresis was rapid, always within 3 hours and often within 1 hour. The major diuretic response persisted for 8 - 12 hours, and a lesser effect was noted up to 36 hours (Fig. 2).

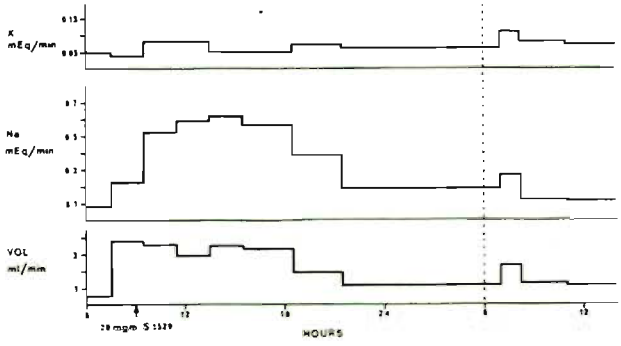

Fig. 2. Duration of diuretic action. Urinary volume, sodium, potassium excretory rates after a single dose of 10 mg S1520 to a normal subject.

Effects of Repeated Daily Administration of S1520

The effects of a daily administration of 10 mg S1520 for 4 consecutive days were determined in a group of 5 normal subjects, and they were compared with measure-

ments on the preceding control day. These included 24-hour urinary volumes, osmolar, sodium, chloride and potassium excretion, serum urea, uric acid, creatinine and osmolality, creatinine and uric acid clearances, body mass and blood pressure. Any untoward symptoms were noted.

The mean value of the 24-hour urinary volume on the control day was 1,49 litres. On the first day of drug therapy, the 24-hour urinary volumes increased in all subjects. The mean increment was 0,6 litres. This increment was not sustained on subsequent days, being 0,34 litre on the second day, 0,11 litre on the third day, and 0,28 litre less than the control volume on the fourth day (Fig. 3). This decrement in urinary volume occurred despite free fluid intake.

All subjects lost mass during the trial (Fig. 4). The mean cumulative mass loss by the third day of S1520 was 1,9 kg and by the fourth day, 1,8 kg. The mass difference between the third and fourth days and the reduction in urinary volume, indicate a tolerance or resistance to the diuretic effect.

The mean value of the osmolar excretion for the control 24 hours was 956 mOsm. On the first day of administering S1520 there was a marked increase in osmolar excretion (Fig. 3), the mean increment being 505 mOsmols. The increments diminished progressively to 356, 110 and 41 mOsm on the second, third and fourth days, respectively, again indicating tolerance.

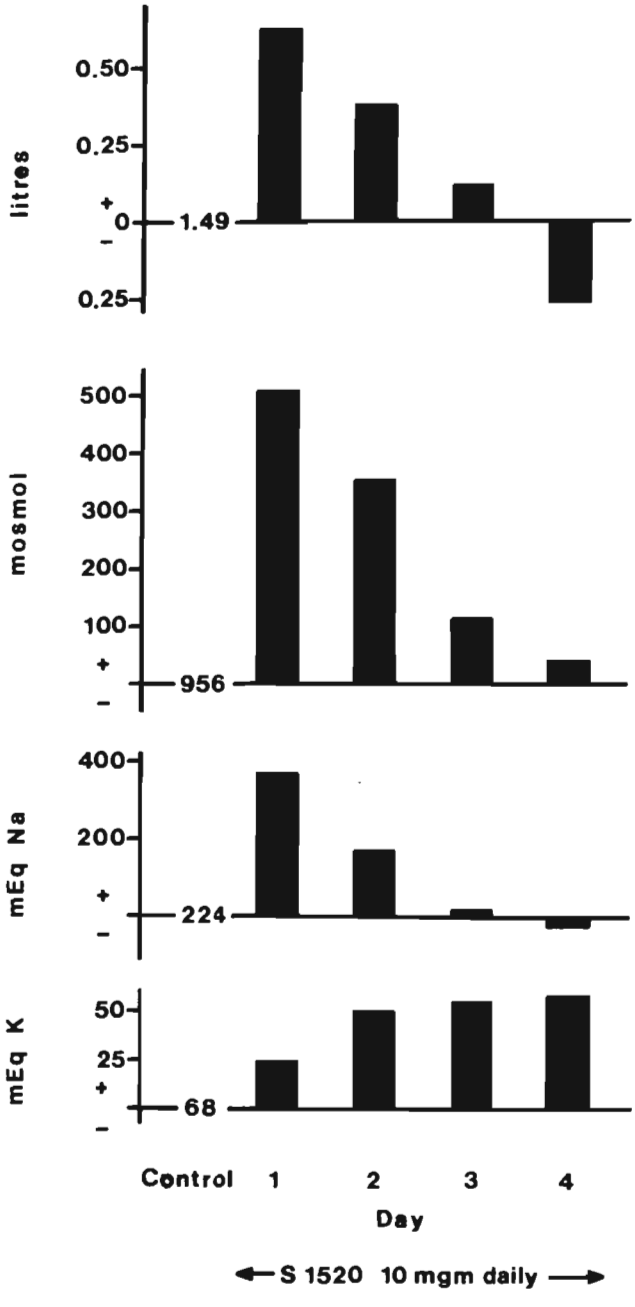

Fig. 3. Diuretic response to the daily administration of 10 mg S1520 in 5 normal subjects. Mean increments above control measurements of 24-hour urinary volume, total osmolar, sodium, and potassium excretion.

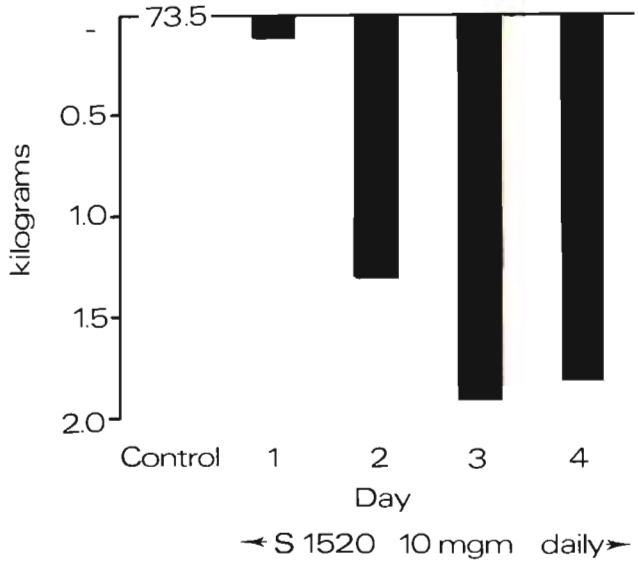

Fig. 4. Cumulative mass loss on 4 days S1520 therapy. Mean values in 5 healthy subjects.

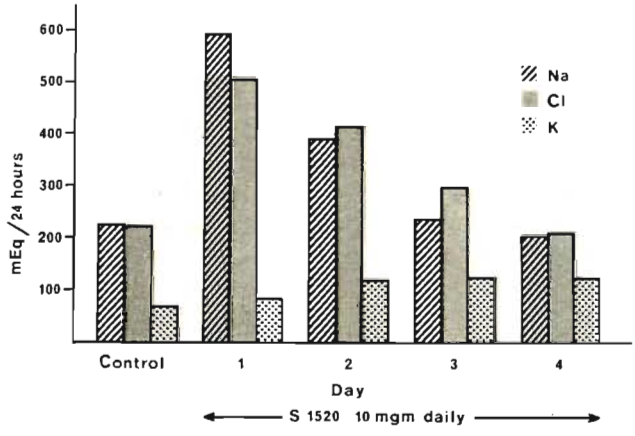

Fig. 5. Twenty-four-hour urinary sodium, chloride, and potassium excretion. Mean values of 5 normal subjects on 10 mg S1520 daily for 4 days.

The mean sodium excretion on the control day was 224 mEq. With S1520 this was increased by 368 mEq on the first day, 164 mEq on the second day, 11 mEq on the third day and was -23 mEq on the fourth day (Fig. 3). Chloride excretion followed the same pattern. Increments above the mean value of 222 mEq for the control day, were 282 mEq on the first day, 189 mEq on the second day, 74 mEq on the third day and -14 mEq on the fourth day (Fig. 5). Chloride excretion exceeded that of sodium on the second, third and fourth days. Potassium excretion increased progressively from day 1 to day 4 (Fig. 3). The control day mean excretion was 68 mEq. The 24-hour increments on S1520 were 15 mEq on day 1, 50 mEq on day 2, 55 mEq on day 3, and 58 mEq on day 4. The increasing potassium excretion occurred as sodium excretion decreased, suggesting the development of secondary aldosteronism and accounted in some measure for the difference in sodium and chloride losses.

Serum urea levels increased in all subjects after 4 days on the drug, from a control mean value of 23,4 to 35,4 mg/100 ml. Serum uric acid levels increased from a control mean value of 6,9 to 7,8 mg/100 ml. Serum creatinine levels were insignificantly affected. Creatinine clearances decreased from a mean value of 107 to 97 ml/min. Uric acid clearances decreased from a mean value of 6,7 to 5,3 ml/min (Table I).

TABLE I. CHANGES IN SERUM UREA, URIC ACID, AND CREATININE CONCENTRATIONS, CREATININE AND URIC ACID CLEARANCES, AFTER 4 DAYS' S1520 IN 5 NORMAL SUBJECTS

	Control day		After 4 days S1520	
	Range	Mean	Range	Mean
Serum urea (mg/100 ml)	13 - 30	23,4	35 - 43	35,5
Serum uric acid (mg/100 ml)	5,8 - 7,9	6,9	6,6 - 9,5	7,8
Serum creatinine (mg/100 ml)	1,1 - 1,4	1,2	1,1 - 1,6	1,3
Creatinine clearance (ml/min)	88 - 142	107	74 - 124	97
Uric acid clearance (ml/min)	4,0 - 9,5	6,7	3,6 - 8,0	5,3

Symptoms were generally mild during the trial. One subject complained of slight breathlessness on exertion and tightness in the chest during the first 3 days of S1520. Two subjects complained of difficulty in visual accommodation during the first 2 days only. All the subjects were normotensive and, apart from minor fluctuations, the blood pressures were unaffected by the drug.

Effects of Water Loading and Dehydration

In a study on 2 normal subjects (Fig. 6), water loads of 20 ml/kg body mass were given, and this state of hydration was maintained by the drinking of water equal in volume to each volume of urine voided. After two-and-a-half hours, when the subjects were in a steady state of maximal free-water clearance with minimal urine osmolality, 20 mg of S1520 were given orally. Over the following 3 hours there was a gradual increase in urine osmolality from 50 to 100 mOsm/kg H_2O, and a decrease in free-water clearance from 14 to 10 ml/min. In another study, after dehydration for 14 hours, 20 mg S1520 was given by mouth and water deprivation maintained. Negative free-water increased as osmolar excretion increased. These experiments indicate that the distal tubule is the probable main site of the drug's diuretic action.[1]

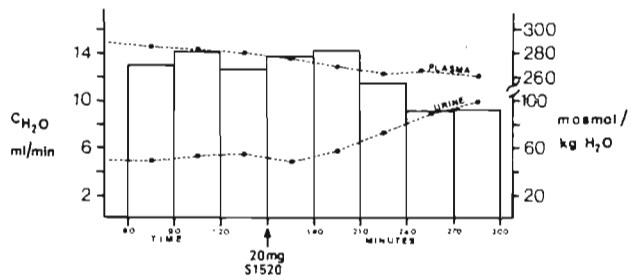

Fig. 6. Effect of 20 mg S1520 on plasma and urinary osmolality and free-water clearance (C_{H_2O}) during a sustained water load of 20 ml/kg body mass.

CLINICAL STUDIES

The therapeutic effect of S1520 was assessed in patients with oedema, and an attempt was made to judge its value as a diuretic in patients with renal failure, and the relative efficacy of S1520 was compared with furosemide.

Twenty-two patients suffering from oedema were studied. Twenty had congestive cardiac failure and 2 cirrhosis of the liver. Sixteen of these patients had normal or only slightly impaired renal function with creatinine clearances greater than 50 ml/min (referred to below as 'normal renal function'). The remaining 6 patients suffered from severe chronic renal failure with creatinine clearances of 12 ml/min, or less.

Conventional therapy for all patients was not interrupted during the trial, i.e. diet, digitalis, anticoagulants, antihypertensive drugs, etc. Only diuretic drugs were withdrawn 24 hours before the administration of the trial drug. This period was used for control purposes.

Diuretic tablets were administered as a routine as a single oral dose at 0800 each day. Ten of the patients with normal renal function were given 20 mg S1520 daily (about 0,25 mg/kg), this dose having been determined as an adequate effective dose in the trial on normal subjects. In the 2 patients with cirrhosis and the 6 with severe chronic renal failure, the dosage of S1520 was increased gradually whenever the therapeutic response was inadequate, to a maximum of 300 mg (about 4,0 mg/kg). In a number of instances S1520 was withdrawn before this dosage was reached because of clinical indications for an alternative therapy. To compare the efficacy of S1520 with furosemide, 4 patients with normal renal function were studied. Twenty milligrams S1520 (A) and 40 mg furosemide (B) were administered in a daily sequence of ABBA or BAAB. These doses were chosen as the 'usual' effective doses for patients with normal renal function. To

the 6 patients suffering from severe renal failure, who had had furosemide therapy before the present trial, the pre-trial dose of furosemide was readministered after the withdrawal of S1520. The hospital records of these 6 patients and 6 patients with congestive cardiac failure and normal renal function who had also had prior furosemide therapy, were used to obtain some information about the nature of their responses to furosemide.

Measurements monitored during the trial included body mass, blood pressure, pulse rate, body temperature, and a clinical examination with particular reference to signs and symptoms of possible side-effects on cardiovascular, central nervous, skin, musculoskeletal and haemopoietic systems, was made. Serial 24-hour urine samples were collected and analysed for urea, creatinine, sodium, potassium, chloride, and osmolar concentrations. Full blood counts, liver function tests, fasting blood glucose, serum uric acid, and creatinine clearances were estimated at the beginning of the trial and 5 days after the start of therapy.

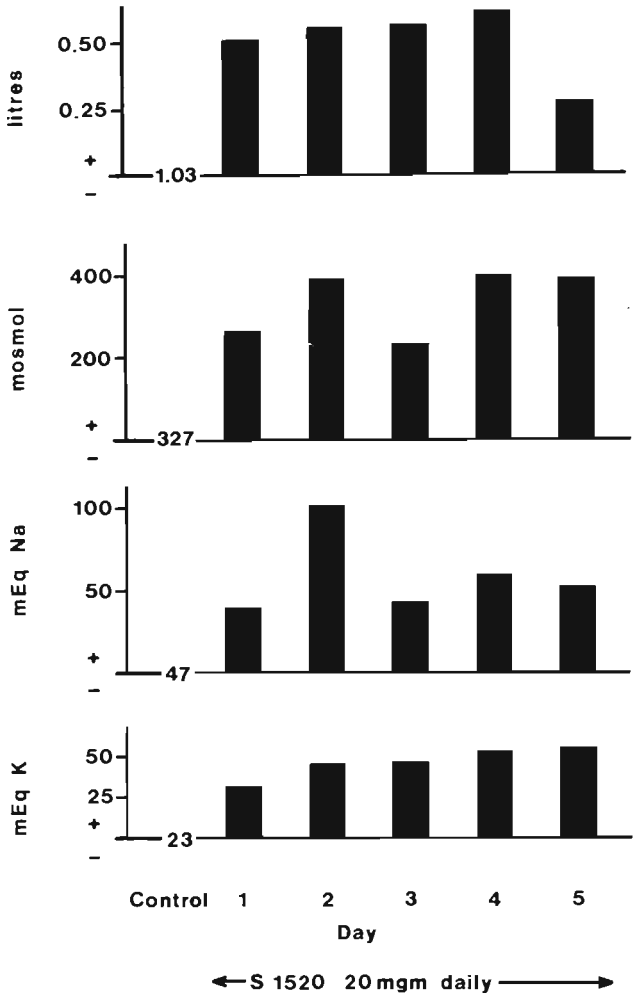

Fig. 7. Diuretic response to the daily administration of 20 mg S1520 in 10 patients suffering from congestive cardiac failure but with normal renal function. Mean increments above control measurements of 24-hour urinary volume, total osmolar, sodium, and potassium excretion.

Patients with Normal Renal Function (Table II)

A good diuretic response was noted in all the patients of this group, excepting the 2 patients with cirrhosis. With continuous therapy in the 10 patients who did respond, the 24-hour urinary volumes, osmolar, and sodium excretions increased and remained greater than the control values for at least 5 days, or for as long as the patients remained oedematous (Fig. 7). The 2 patients with cirrhosis suffered from dilutional hyponatraemia as a result of water overload, the serum sodium concentrations being 110 mEq/L in one patient and 122 mEq/L in another; both failed to lose mass despite increased dosage. Subsequent furosemide therapy was equally ineffective, and severe fluid restriction was imposed on these patients to control their oedema.

Patients with Severe Renal Failure (Table III)

S1520 was considered therapeutically inadequate in the 6 patients of this group because increasing dosage failed to achieve a diuretic response. The daily doses were increased to 300 mg in 2 patients, 200 mg in 2 patients, and to 120 and 40 mg in the remaining 2 patients. The increasing dosage of S1520 had to be abandoned in each case because of increasing oedema and a clinical indication for alternative therapy. Only 1 patient lost mass while on S1520. This, however, resulted from very severe restriction of fluid intake and mild diarrhoea. In 2 of the patients the 24-hour urinary sodium excretion increased by 14 and 6 mEq above the control levels, but these small increases were of no therapeutic consequence.

RELATIVE EFFICACY OF S1520 AND FUROSEMIDE

Patients with Normal Renal Function (Table IV)

Although the original intention was to study more patients in the sequence ABBA and BAAB, the study was restricted to a group of only 4 patients for reasons mentioned in the discussion below. Superficially it appears that the diuretic effect was equivocal in 1 patient, greater with S1520 in 1 patient, and greater with furosemide in the remaining 2 patients.

Patients with Severe Renal Failure (Table III)

All patients of this group were given furosemide after the withdrawal of S1520. In 5 patients in whom it was measured, the natriuresis was greater with furosemide than with S1520. An increased sodium excretion is presumed to have occurred in the sixth patient, because of an obvious diminution in the oedema. Apart from this case, the clinical responses to furosemide were poor and only marginally superior to S1520. Three of the patients were subsequently subjected to peritoneal dialysis to correct sodium and water overload.

TABLE II. RESPONSES TO S1520 IN 12 OEDEMATOUS PATIENTS WITH NORMAL RENAL FUNCTION

Age (years)	Sex	Creatinine clearance (ml/min)	S1520 therapy (mg/24 h)	Duration of S1520 therapy (days)	Body mass (kg)		Blood pressure (mmHg)		Blood urea (mg/100 ml)		Serum uric acid (mg/100 ml)		Fasting blood glucose (mg/100 ml)		Serum K (mEq/L)		K supplementation (g/24 h)	Diuretic response
					A	B	A	B	A	B	A	B	A	B	A	B		
64	M	57	20	8	71,0	61,9	110/70	110/80	30	26	6,8	6,9	135	112	4,0	3,9	—	Good
67	M	70	20	12	79,4	75,5	140/90	120/70	36	43	6,5	7,5	106	114	4,0	4,8	1,8	Good
66	F	51	20	4	74,0	71,0	120/80	130/80	42	47	6,4	7,6	146	110	4,3	4,0	3,6	Good
67	M	81	20	5	81,4	76,7	100/60	100/60	16	14	3,7	4,5	83	90	3,9	3,6	1,8	Good
79	F	57	20	5			110/60	120/70	46	46	6,0	7,4	120	134	4,3	4,7	—	Good
68	F	51	20	4	50,5	46,8	110/70	120/90	59	33	7,9	7,4	93	89	4,9	3,3	—	Good
28	F	53	20	4	50,4	46,2	140/90	140/90	41	43	5,4	5,1	116	120	4,0	4,3	3,6	Good
63	M	56	20	4	86,8	82,0	110/70	120/70	52	40	6,0	6,7	110	112	5,0	5,2	—	Good
62	M	60	20	5	81,5	77,0	130/90	120/90	50	46	6,4	6,6	106	108	4,5	4,0	—	Good
78	M	52	20	5	75,0	71,0	130/80	130/80	41	38	7,1	7,0	94	98	3,5	4,2	—	Good
50	M*	60	40	4	114,0	116,0	110/40	110/40	63	75	14,4	17,0	114	118	6,4	4,0	—	Ineffective
50	F*	50	200	13	44,5	45,0	100/60	100/60	33	36	7,4	6,0	92	103	5,3	5,2	—	Ineffective

A = before therapy; B = after therapy.
* Patient with cirrhosis and hyponatraemia.

TABLE III. RESPONSES TO S1520 AND SUBSEQUENT FUROSEMIDE THERAPY IN 6 OEDEMATOUS PATIENTS SUFFERING FROM SEVERE CHRONIC RENAL FAILURE

Sex	Age	Aetiology of renal failure	Creatinine clearance (ml/min)	Maximum dose S1520 (mg/24 h)	Duration of therapy (days)	Body mass (kg)		Urinary sodium (mEq/24 h)		Diuretic response	Furosemide dosage (mg/24 h)	Maximum urinary sodium (mEq/24 h)
						A	B	A	B			
F	74	Chr. pyelo.	12	40	4	55,7	56,0	62	58	Ineffective	120	
M	34	Chr. pyelo.	2	120	3	66,1	67,5	5	19	Ineffective	1 000	45
M	50	Chr. GN	2	300	4	84,0	78,3	27	33	Ineffective	1 000	44
M	50	Chr. GN	2	300	4	71,0	71,8	14	9	Ineffective	1 000	14
F	38	DLE	5	200	2	50,5	53,0	18	5	Ineffective	1 000	59
F	43	Analgesic N	2	200	2	48,5	48,5	33	19	Ineffective	1 200	65

A = control measurement before S1520 therapy; B = after S1520 therapy.

Toxic and Side-Effects

S1520 appeared to be free of significant toxic or side-effects during the trial. In the patients with normal renal function, potassium excretion increased progressively to the fifth day of therapy, from a mean control value of 23, to 76 mEq/24 h (Fig. 7). This was not associated with any marked hypokalaemia over the test period. Mean serum potassium levels decreased from 4,5 to 4,3 mEq/litre. This tendency for the serum potassium level to fall was greater in patients who did not receive potassium supplements (Table II). Hyponatraemia attributable to

TABLE IV. LATIN-SQUARE COMPARISON OF 24-HOUR DIURETIC RESPONSES TO 20 mg S1520 AND 40 mg FUROSEMIDE IN 4 PATIENTS WITH NORMAL RENAL FUNCTION SUFFERING FROM CONGESTIVE CARDIAC FAILURE

Patient		Day 1	Day 2	Day 3	Day 4	
1	Diuretic	A	B	B	B	
	24-h urinary sodium (mEq)	118	136	66	25	
	24-h urinary volume (ml)	1 020	1 640	1 320	1 680	Equivocal
2	Diuretic	B	A	A	B	
	24-h urinary sodium	40	236	167	79	
	24-h urinary volume	1 580	2 780	1 920	1 260	S1520
3	Diuretic	A	B	B	A	
	24-h urinary sodium	142	192	251	173	
	24-h urinary volume	1 650	1 800	1 920	1 700	Furosemide
4	Diuretic	B	A	A	B	
	24-h urinary sodium	225	216	228	341	
	24-h urinary volume	2 650	2 030	1 620	2 360	Furosemide

A = 20 mg S1520; B = 40 mg furosemide.

diuretic action was not observed. The mean control serum sodium was 131,3 mEq/litre, and after 5 days it was almost unaltered at 131,0 mEq/litre. Serum uric acid levels increased in 8 of the 12 patients, the mean being 7,0 mg/100 ml before S1520 and 7,5 mg/100 ml after 5 days of treatment. Increases ranged from 0,1 to 3,0 mg/100 ml (Table II). No gouty symptoms were encountered. Blood glucose levels were marginally increased in 9 of the 12 patients. The increases ranged from 2 to 14 mg/100 ml (Table II). In no case was glycosuria or ketosis noted. No significant changes occurred in haemoglobin, red cell, total, differential white cell, or platelet counts. Liver function tests, including serum bilirubin, flocculation tests, serum enzymes and serum proteins, were unaffected. No abnormal gastro-intestinal or nervous symptoms were noted and no hypersensitivity reactions were encountered.

DISCUSSION

S1520 appears to be a safe and effective diuretic and is well tolerated by patients. It has most of the general pharmacological properties associated with distally acting diuretics such as the benzothiazides and chlorthalidone. The responses noted in the patients with normal renal function were similar to those seen in the normal volunteers studied, in that the drug was rapidly effective when given orally and had an action which persisted for up to 36 hours. Kaliuresis was usually progressive, and monitoring of patients to determine the need for potassium supplementation, is necessary. Predictably, S1520 was found to be ineffective in severe renal failure; this is a feature common to all diuretics of this class.

The early tolerance to S1520 noted in the normal subjects is no doubt related to the fact that with sodium depletion, sodium is very avidly reabsorbed by the proximal tubule, allowing relatively little to reach that portion of the tubule where it could be affected by a distally acting diuretic.[2] Secondary aldosteronism which develops also antagonises the diuretic action. In this regard early tolerance was not seen in the patients with oedema. The diuretic response persisted as long as they were oedematous; it is presumed that they would develop some resistance when sodium-depleted. This phenomenon is not regarded as a disadvantage for a maintenance diuretic, as it safeguards the patient against too severe sodium depletion. The results of the Latin-square observations on the 4 patients in whom S1520 was compared on the ABBA, BAAB basis, are not easy to interpret. It is difficult to decide what doses of trial drugs can be usefully compared if the drugs act at different sites and involve different mechanisms, as their duration of action varies greatly. In the trial on normal subjects 20 mg S1520 produced a response of near-maximal efficacy. This dose was compared empirically with 40 mg furosemide which is far below the maximal effective dose for this drug. It was pointless to go on increasing the dose of furosemide to compare the effects in patients with normal renal function, as progressively increasing diuresis would occur as long as effective renal function persisted. When furosemide follows S1520, an increase may be due in part to summation with the prolonged action of S1520. Also, with clinical improvement that is usually rapid with diuretics in patients with normal renal function, the efficacy of furosemide would be less affected by progressive sodium depletion. For these reasons the Latin-square comparison was discontinued after the fourth patient. However, from the few observations made, together with the evidence obtained from the patients' records, there is no doubt that the maximal efficacy of furosemide is greater.

In these short-term studies no significant effects on blood pressure were noted. A much longer period of study in hypertensive patients without oedema would be necessary to determine the usefulness of S1520 as an antihypertensive agent.

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